REMARKS

Favorable reconsideration is respectfully requested in view of the following remarks. Claims 1-7 are pending.

Information Disclosure Statement (IDS)

With regard to the IDSs that were filed on March 15, 2010 and April 13, 2010, the following references were crossed out as not being considered because a concise explanation was not provided: (1) Prosecution documents of H21 (Gyo-ke) 10107; (2) Prosecution documents of H21 (Gyo-ke) 10420; and (3) Demandant's 6th Brief for H21 (Gyo-ke) 10107. Applicants note that a concise explanation was already provided for references (1) and (2) in the IDS that was filed on March 15, 2010, and therefore, references (1) and (2) are not included in the enclosed SB08 form. However, for the Examiner's convenience, the concise explanation of references (1) and (2) is provided again for the Examiner's convenience. A clean copy of Form SB08 is also provided.
Concise explanation for Documents (1) and (2):
"These documents are related to a suit for canceling trial decision of Mukou (Invalidation) 2008-800293 (invalidation trial case of JP 3897805) that was filed by Eiken Kagaku Kabushiki Kaisha (demandant). Although the demandant submitted documents describing the reasons for canceling the trial decision, they did provide any new evidence in these documents. The defendant explained in the suit for canceling trial decision of Mukou (Invalidation) 2008-800091 (invalidation trial case of JP 3867926) that the demandant's arguments were technically wrong, and, the experimental data submitted by the demandant on January 19, 2010 was inappropriate. The experimental data submitted by the defendant is the same as Experiment I in the Declaration prepared and filed in co-pending matter Serial No. 10/532975 in response to the US Office Action dated July 29, 2009."

With regard to reference (3), a concise explanation for this reference is provided below. Reference (3) is included in the enclosed SB08 form (NPL 10).
Concise explanation for Document (3):

"In this document, it is explained that the argument of the demandant in Suite Against Trial Decision of Mukou (Invalidation) 2008-800091 (invalidation trial case of JP 3867926) is technically incorrect and the experimental data (Declaration) submitted by the demandant on January 19, 2010 is inappropriate. The description of the experimental data (Declaration) submitted by the demandee this time is the same as that of Experiment I of the Declaration submitted at the time of responding to the Office Action dated July 29, 2009."

With regard to the IDS filed on October 12, 2010, Applicants note that the IDS filed on October 12, 2010 includes the Canadian Office Action. The references cited in the Canadian Office Action already have been considered by the Examiner, and therefore, filing of another IDS including the Canadian Office Action is not necessary.

Claim Rejections – 35 USC 103

Claims 1-5 are rejected under 35 USC 103(a) as being unpatentable over EP 0971039A2 (Rabbani et al.) in view of WO 96/001327 (David et al.). Applicants respectfully traverse the rejection.

Claim 1 recites a first primer that contains, in its 3' end portion, a sequence (Ac') that hybridizes to a sequence (A) located in the 3' end portion of the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Ac'), a sequence (B') that hybridizes to a complementary sequence (Bc) to a sequence (B) that is present on the 5' side with respect to the sequence (A) in the target nucleic acid sequence (hereinafter, the first primer will be referred to as a "turn-back primer" or "TP"). Claim 1 further recites a second primer that contains, in its 3' end portion, a sequence (Cc') that hybridizes to a sequence (C) located in the 3' end portion of a complementary sequence to the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Cc'), a folded sequence (D-Dc') that contains, on the same strand, two nucleic acid sequences that hybridize to each other (hereinafter, the second primer will be referred to as a "folded primer" or "FP").

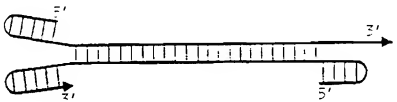
Rabbani and David do not disclose or suggest the features of claim 1. Even if Rabbani discloses a TP as recited in claim 1, which is not conceded, it does not disclose a

primer set that includes the TP and the FP as recited in claim 1. Rather, Rabbani at best discloses the use of a TP-TP primer set. David may disclose a FP as recited in claim 1, but does not disclose a primer set that includes the TP and the FP as recited in claim 1. Rather, David at best discloses the use of a FP-FP primer set. The combination of Rabbani and David does not disclose or suggest the features of claim 1.

The rejection contends that it would have been obvious to have extended the teachings of Rabbani to include the known alternative hairpin primer format of David to arrive at the claimed invention with a reasonable expectation of success. However, the rejection's interpretation of Rabbani and David is incorrect.

Firstly, David involves the design of primers which perform their intended function in conditions that are completely different from the conditions in which Rabbani's primers are intended to perform their function. That is, David teaches an amplification mechanism for their primers where at least two thermal denaturing steps are required for annealing of their primers.

Specifically, as shown in Figure 5a of David, a thermal denaturing step is performed to separate the template strands. The reaction mixture is then cooled so as to allow the P1 primer to anneal and the DNA polymerase to form an extended strand as shown in Figures 5b-5d. After formation of the extended strand as shown in Figure 5d, the template strand and the extended strand are then separated by another thermal denaturing step as shown Figure 5e. The reaction mixture is then cooled again so as to allow the P2 primer to anneal and the DNA polymerase to form an extended strand as shown in Figures 5f-5h. The two thermal denaturing steps are critical to form the double folded portions on the left-hand side of the double strand as shown in Figure 5h (the double strand with the double folded portions on the left-hand side shown in Figure 5h is reproduced below).



As is apparent from Figures 5i-5m of David, amplification can proceed without any further thermal denaturing steps, but this is only possible only where at least two thermal denaturing steps are conducted and the double strand with the double folded portions as shown above is formed.

On the other hand, Rabbani teaches a design of primers that require only one initial thermal denaturing step. Specifically, as shown in step 1 of Figure 1, after an initial thermal denaturing step, a hairpin loop-forming primer is allowed to anneal to the separated strand after cooling the mixture. Due to the special design of the hairpin loop-forming primer, another hairpin loop-forming primer is allowed to anneal without another thermal denaturing step.

As shown in Figures 7 and 8 of Rabbani, intricate structures are formed from the spontaneous amplification reaction propagated by the loop-forming primers, and these intricate structures allow spontaneous amplification to continue. In view of this understanding, one skilled in the art of isothermal amplification as taught by Rabbani would generally avoid conducting a denaturing step after the initial thermal denaturing step due to the possible disruption of continued spontaneous amplification by thermal heating of the reaction products having intricate structures that are formed from the spontaneous amplification reaction propagated by the loop-forming primers. Thus, one skilled in the art of designing primers for amplification conditions that involve only one initial thermal denaturing step as taught by Rabbani, would not turn to the design of primers that require thermal heating of the reaction mixture after the amplification reaction has already been initiated by an initial thermal denaturing step as taught by David.

Even further, it is clear from the reaction mechanism shown in Figures 5a to 5h that the design of David's primers is such that both the P1 and P2 primers must have a folded sequence in order to achieve the intended reaction mechanism.

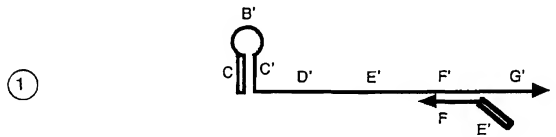
Specifically, as shown in Figures 5a-5i, due to the folded sequence in P1, the double folded portions in the first double strand as shown in Figure 5h can be formed. The double folded portions are necessary to separate the first double strand without utilizing another thermal denaturing step. As shown in Figure 5j, the intended outcome

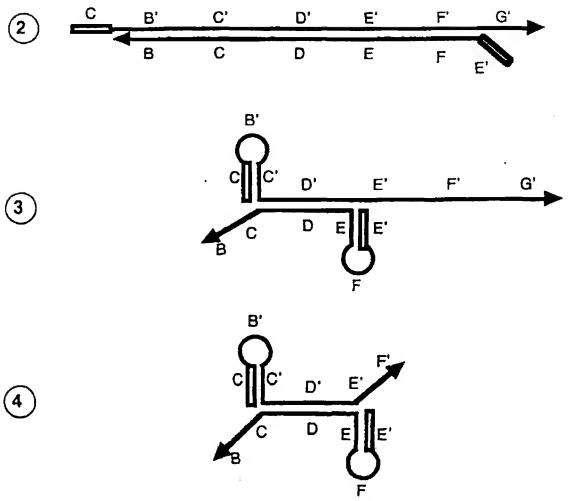
after separation of the double strand is to form a second double strand with double folded portions on the right-hand side as shown in Figure 5j. It is apparent from the amplification mechanism depicted in Figures 5f to 5j that a folded sequence in P2 is necessary to form the second double strand with the double folded portions on the right-hand side shown in Figure 5j.

Thus, it is clear from the above that David teaches that both the P1 and P2 primers must have the same structures, that is, a symmetrical primer set must be used to achieve the intended reaction mechanism as shown in Figures 5a to 5m. David does not provide any guidance as to a reaction mechanism or experimental data showing that successful amplification can be achieved using asymmetrical primers.

Therefore, given that David teaches that if a primer with a folded sequence is used, a symmetrical primer set is required to achieve successful amplification, and further given that David teaches the requirement of reaction conditions that are completely different from those of Rabbani to achieve the intended function of their primers, there would not have been a reasonable expectation of success in using an asymmetrical primer set containing one of David's primers under amplification conditions as taught by Rabbani and achieving successful amplification.

The rejection refers to Figure 4 and contends that Figure 4 of Rabbani alone suggests a combination of primers. However, Figure 4 in no way shows a combination of primers. Figure 4 shows the following four steps:





In the above four steps, only step 1 shows a primer, namely the primer having the sequence E' and F.

The rejection's understanding appears to be that the strand having the sequence BCDEFE' shown in steps 3 and 4 is a primer. However, as explained previously with reference to pages 11 and 12 of the Technical Explanation submitted with the Supplemental Amendment filed on August 16, 2010 (for the Examiner's convenience, a copy of the Technical Explanation is enclosed), the elongated strand that is formed from the TP is not a primer. In Figure 4, the primer having the sequence E' and F is the TP. The strand having the sequence BCDEFE' shown in step 2 is a strand that is synthesized from the primer having the sequence E' and F binding to the target sequence in step 1. The strand having the sequence BCDEFE' shown in steps 3 and 4 corresponds to the

strand having the sequence BCDEFE' shown in step 2. The difference is that the strand having the sequence BCDEFE' shown in steps 3 and 4 has formed a hairpin loop. Therefore, the strand having the sequence BCDEFE' shown in steps 2, 3 and 4 is an elongated strand, and is not a primer. Thus, Figure 4 of Rabbani does not teach a combination of primers.

The rejection then contends that given the teachings in Figure 4, and further given that Rabbani teaches that the first and second primers in the primer set can be the same or different, it would have been obvious to use the primer as taught by David as the second primer in Rabbani and achieve the features of claim 1. However, as indicated above, Figure 4 of Rabbani shows the use of only one primer, and does not disclose or suggest the use of a combination of primers. Moreover, Rabbani provides only an example of the second primer being TP, and does not provide any other guidance as to the structure of the second primer other than that it should anneal to the target sequence. Further, one skilled in the art of designing primers for amplification conditions that involve only one initial thermal denaturing step as taught by Rabbani, would not turn to the design of primers that require thermal heating of the reaction mixture after the amplification reaction has already been initiated by an initial thermal denaturing step as taught by David. Even further, given that David teaches that a symmetrical primer set is required to achieve successful amplification when using FP primers, and further given that David teaches the requirement of reaction conditions that are completely different from those of Rabbani to achieve the intended function of their primers, there would not have been a reasonable expectation of success in using an asymmetrical primer set containing one of David's primers under amplification conditions as taught by Rabbani and achieving successful amplification.

Additionally, the advantageous effects of claim 1 would not have been expected from the combination of Rabbani and David. As explained previously with reference to the Technical Explanation submitted with the Supplemental Amendment filed on August 16, 2010, Applicants have found that when a TP-FP primer set in accordance with claim 1 is used, an amplification mechanism can be achieved such that exponential non-specific amplification seen with a TP-TP primer set does not occur. The effects of the

amplification mechanism is that background noise (non-specification amplification) can be reduced and the signal-to-noise ratio can be increased significantly so as to improve the detection of single nucleotide polymorphisms (SNPs) as compared to when only TPs are used. Such advantageous effects of claim 1 would not have been expected from Rabbani and David. Accordingly, claim 1 and its dependent claims are patentable over the references.

Claims 5-7 have been rejected as unpatentable over Rabbani et al. in view of David et al., as applied to claims 1-5 above, and further in view of Genome Research (Pastinen et al.). Applicants respectfully traverse the rejection.

Claim 1 has been distinguished above over Rabbani and David. Pastinen does not remedy the deficiencies of Rabbani and David. Claims 5-7 depend from claim 1 and are patentable over the references for at least the same reasons discussed above. Applicants do not concede the correctness of the rejection.

In view of the foregoing, favorable reconsideration in the form of a notice of allowance is requested. Any questions or concerns regarding this communication can be directed to the attorney-of-record, Douglas P. Mueller, Reg. No. 30,300, at (612) 455.3804.

Respectfully submitted,

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